SUPPLEMENTARY DATA

Appendix - List of Participating Investigators

Study comparing LY IGlar to EU-approved IGlar (NCT01476345): Maria M. Ferreira, MFamMed; PAREXEL International Bloemfontein Early Phase Unit, Bloemfontein, South Africa

Study comparing LY IGlar to US-approved IGlar (NCT01688635) and study comparing EU- to US-approved IGlar (no trial registration number because the study does not involve an investigational product): Chew Lan Chong, MRCP, MSc; Lilly-NUS Centre for Clinical Pharmacology, Singapore, Singapore

Online-Only Supplemental Material

Note to the editor: In order to condense the results of 3 Phase 1 trials into a single manuscript, it was necessary to focus on the most key data obtained during the trials. These supplemental materials are therefore provided in the interests of transparency, to allow the interested reader to access additional trial data not included in the main manuscript and to satisfy principles of honesty, openness, and integrity in the publication of clinical trial data.

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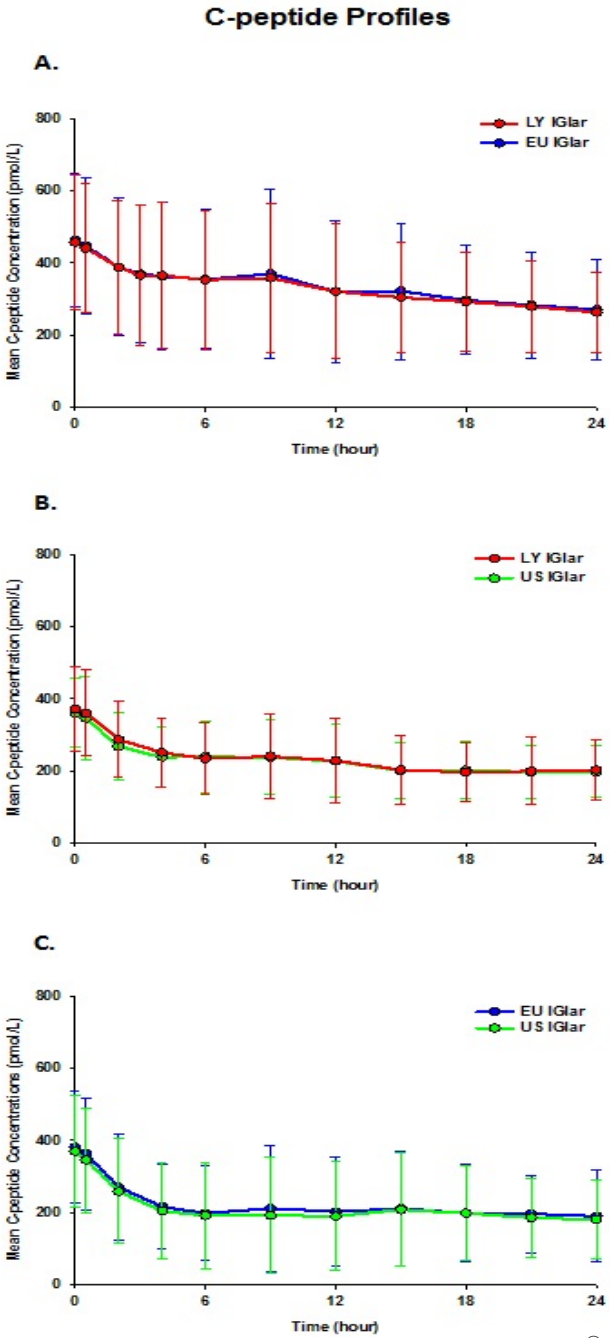
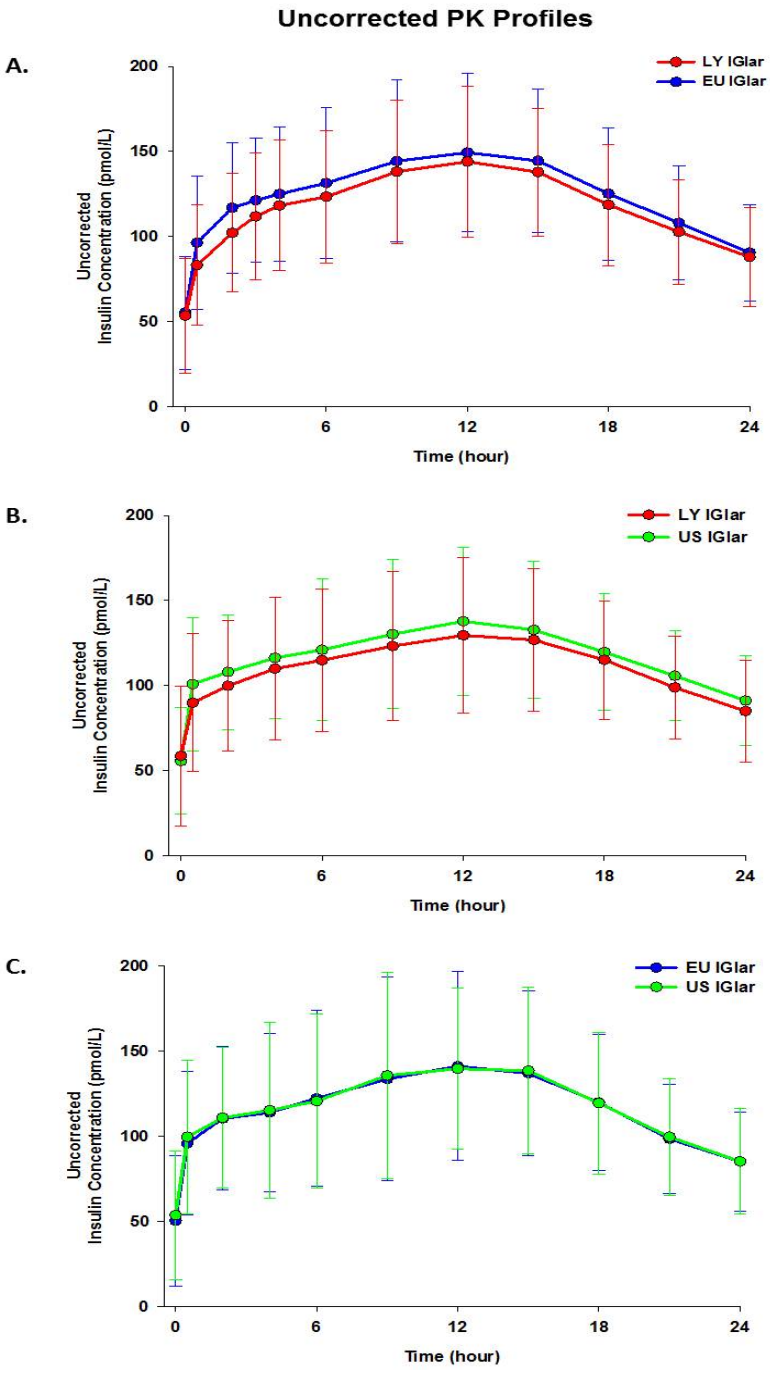
Supplementary Figure S1. Mean (±Standard Deviation) C-peptide Concentrations following Subcutaneous Administration of 0.5 U/kg LY IGlar, EU-approved IGlar, or US-approved IGlar



Abbreviations: EU = European Union; IGlar = insulin glargine (Lantus®); LY IGlar = LY2963016; US = United States.

SUPPLEMENTARY DATA

Supplementary Figure S2. Mean (±Standard Deviation) Serum Insulin Concentrations (no C-peptide Correction) following Subcutaneous Administration of 0.5 U/kg LY IGlar, EU-approved IGlar, or US-approved IGlar



Abbreviations: EU = European Union; IGlar = insulin glargine (Lantus®); LY IGlar = LY2963016; PK = pharmacokinetic; US = United States.

Plots of mean serum insulin (LY IGlar or IGlar [Lantus®]) concentration in the 24 hours following 0.5-U/kg SC administration of 3 insulin glargine products (Plots A, B, and C are from 3 separate studies conducted in separate groups of subjects).

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Supplementary Table S1. Summary of the Secondary Pharmacokinetic Parameters of LY IGlar, EU-approved IGlar, and US-approved IGlar

Treatment (0.5 U/kg)	Geometric Mean (CV%)	N
AUC(0-∞) (pmol·h/L)		
LY IGlar	2590 (46)	88
US IGlar	3060 (46)	89
LY IGlar	2830 (39)	80
EU IGlar	2930 (41)	80
EU IGlar	2890 (44)	40
US IGlar	2950 (44)	40
$t_{1/2}$ (h)		
LY IGlar	10.0 (59)	88
US IGlar	11.6 (69)	89
LY IGlar	9.95 (66)	80
EU IGlar	9.76 (61)	80
EU IGlar	9.35 (62)	40
US IGlar	9.52 (46)	40
CL/F (L/h)		
LY IGlar	81.0 (49)	88
US IGlar	68.4 (48)	89
LY IGlar	78.5 (46)	80
EU IGlar	75.8 (45)	80
EU IGlar	69.3 (47)	40
US IGlar	67.6 (43)	40
V_z/F (L)		
LY IGlar	1170 (58)	88
US IGlar	1140 (55)	89
LY IGlar	1130 (58)	80
EU IGlar	1070 (58)	80
EU IGlar	935 (50)	40
US IGlar	929 (46)	40

Abbreviations: AUC(0-∞) = area under the concentration-time curve from zero to infinity; CL/F = total body clearance of drug calculated after extra-vascular administration; CV% = coefficient of variation; EU = European Union; IGlar = insulin glargine (Lantus®); LY IGlar = LY2963016; N = number of subjects; t1/2 = half-life associated with the terminal rate constant in noncompartmental analysis; US = United States; Vz/F = apparent volume of distribution during the terminal phase after extra-vascular administration.

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Supplementary Table S2. Summary of the Secondary Pharmacodynamic Parameters of LY IGlar, EU-approved IGlar, and US-approved IGlar

Treatment (0.5 U/kg)	Median	Range
TR_{max} (h)		
LY IGlar	12.0	3.00 - 24.0
US IGlar	12.9	3.30 - 24.0
LY IGlar	11.4	0.50 - 17.9
EU IGlar	11.1	0.60 - 17.6
EU IGlar	13.3	4.30 - 24.0
US IGlar	13.6	3.90 - 24.0
T_{onset} (h)		
LY IGlar	2.10	0.22 - 9.77
US IGlar	1.70	0.28 - 23.3
LY IGlar	0.81	0.10 - 3.33
EU IGlar	0.83	0.08 - 3.50
EU IGlar	2.13	0.42 - 13.4
US IGlar	1.87	0.53 - 9.05
Early $TR_{max50\%}$ (h)		
LY IGlar	5.46	1.14 - 19.8
US IGlar	4.66	1.67 - 23.2
LY IGlar	3.13	0.19 - 9.21
EU IGlar	2.84	0.25 - 8.42
EU IGlar	5.17	1.99 - 20.0
US IGlar	5.29	1.32 - 19.8
Late $TR_{max50\%}$ (h)		
LY IGlar	18.8	6.87 - 23.9
US IGlar	18.8	6.62 - 24.0
LY IGlar	21.1	1.28 - 24.0
EU IGlar	22.0	1.63 - 24.0
EU IGlar	19.7	8.47 - 24.0
US IGlar	19.7	4.46 - 23.8
T_{last} (h)		
LY IGlar	24.0	13.9 - 24.2
US IGlar	24.0	11.7 - 24.1
LY IGlar	23.8	23.3 - 24.0
EU IGlar	23.8	21.0 - 24.0
EU IGlar	24.0	20.0 - 24.1
US IGlar	24.0	22.5 - 24.1
GIR_{last} (mg/kg/min)*		
LY IGlar	0.950	79
US IGlar	1.05	73
LY IGlar	1.06	86
EU IGlar	1.15	86
EU IGlar	0.828	149
US IGlar	0.751	138

Abbreviations: early TRmax50% = time to 50% maximal GIR before TRmax; GIR = glucose infusion rate; GIRlast = value of last measurable GIR; late TRmax50% = time to 50% maximal GIR after TRmax; Tlast = time of last measurable GIR; Tonset = time of first change of GIR postdose; TRmax =

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time to maximum GIR.

* Geometric mean (coefficient of variation)